REMARKS/ARGUMENTS

The Pending Claims

Claims 36, 37, and 40-70 are pending and are directed to a bacterial artificial chromosome (BAC) and a method of producing and mutagenizing same.

The Office Action

Claims 36, 37, and 40-70 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Messerle et al., *J. Mol. Med.*, *74*: B8 (1996) ("the Messerle reference") and Kemble et al., *J. Virol.*, *70*: 2044-2048 (1996) ("the Kemble reference") alone or in combination with one or more of the following secondary references: Ehtisham et al., *J. Virol.*, *67*: 5247-5252 (1993) ("the Ehtisham reference"), Gage et al., *J. Virol.*, *66*: 5509-5515 (1992) ("the Gage reference"), Chen et al., *Mol. Cell. Biol.*, *7*: 2745-2752 (1987) ("the Chen reference"), and Luckow et al., *J. Virol.*, *67*: 4566-4579 (1993) ("the Luckow reference"). Reconsideration of these rejections is respectfully requested.

Discussion of Rejections Under 35 U.S.C. § 103

Claims 36, 37, and 40-70 have been rejected under Section 103 as allegedly unpatentable over the combination of the Messerle reference and the Kemble reference alone or in combination with one or more secondary references. These rejections are traversed for the reasons set forth below.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the pending claims, is unobvious in view of the cited references.

Regarding the scope and content of the prior art, the Messerle reference discloses an attempt to clone a full length MCMV genome (about 235 kb) as a BAC in *E. coli*. Specifically, the Messerle reference discloses the generation of a recombinant MCMV virus containing a BAC-vector integrated into the MCMV genome. The circularized or linear recombinant virus was electroporated in *E. coli* strain DH10B. Both of the resulting plasmids contain deletions in the conserved region of about 15 kb. Therefore, none of the resulting BAC-plasmids comprises all the genes that are essential for the generation of an infectious virus, as required by the pending claims. This is further evidenced by the fact that transfection of each of the BAC plasmids alone did not result in any infectious progeny. Rather, only the co-transfection of both plasmids led to plaque formation due to complementation between the deficient BAC plasmids.

The Kemble reference discloses the co-transfection of overlapping cosmids in human fibroblast cells in order to generate recombinant CMV *virus*. In particular, the Kemble reference discloses that wild type CMV Towne is generated using eight cosmids, prior to using an altered cosmid to generate recombinant virus. In this respect, the Kemble reference states:

> The eight cosmids constituting the Towne genome were digested with PacI to **release the intact viral insert from the cosmid vector**, combined, extracted with phenol-chloroform, and precipitated with ethanol. A $CaPO_4$ precipitate was formed from approximately 16 mg of this mixture and transfected onto 10^6 low-passage (>15 passes) HF cells that had been trypsinized and reseeded 3 to 5 h prior to the addition of the DNA. At 2 to 3 weeks following transfection, **plaques** with characteristic CMV cytopathic effect were observed, and the virus derived from this transfection had a restriction pattern characteristic of Towne (data not shown)

(page 2044, right column, third paragraph, emphasis added).

The overlapping inserts disclosed in the Kemble reference reconstituted the entire viral genome (CMV Towne), and were released from the vector by restriction digest. The Kemble reference then discloses that the mixture of the released inserts (i.e., there is no

vector introduced into the cells for recombination) was transfected into cells. After 2-3 weeks, plaques (i.e. *live virus*) were observed, and virus was isolated and analyzed by restriction digest. The isolated virus was found to have the restriction pattern of wild type CMV Towne (that is, without any additional vector sequences).

For the sake of argument and for purposes of the present analysis, one of ordinary skill in the art can be assumed to be someone with an advanced degree and a few years of experience in the relevant art.

With respect to the differences between the claimed invention and the cited references, Applicants note that the Messerle reference does not disclose or suggest a BAC containing all genes essential for the generation of an infectious herpes virus in a host cell, wherein the host cell does not contain any herpes virus genes or herpes virus proteins.

The Kemble reference also does not disclose or suggest the generation of a BAC containing all genes essential for the generation of an infectious herpes virus in a host cell, wherein the host cell does not contain any herpes virus genes or herpes virus proteins. Rather, the Kemble reference discloses the generation of a *recombinant virus*, not a *vector* containing bacterial nucleic acid sequences. In other words, the Kemble reference does not disclose a BAC, but an entire live recombinant *virus*. The recombinant virus disclosed in the Kemble reference does not package itself in the form of a cosmid (or any other bacterial vector). Instead, it packages itself as a live virus without any remaining vector sequences.

There are several reasons why the Kemble reference does not result in the production of infectious vectors, much less infectious BACs. First, co-transfecting cosmids in eukaryotic cells, as disclosed in the Kemble reference, would result in recombination events between the cosmid backbones that carry particular inserts. Such recombination events would produce a "puzzle" of virus inserts and vector backbones. As such, the likelihood of obtaining eight inserts in the correct order are very low.

Moreover, one of ordinary skill in the art would not be able to recognize a successful recombination event (or more precisely a successful series of recombination events) using the technique disclosed in the Kemble reference, other than by purifying virus from plaques. Thus, even if one of ordinary skill in the art were to transfect entire BACs into cells (not

merely the inserts) and obtain the correct recombination events, the recombinant *virus* that is ultimately packaged using the method of the Kemble reference would not include *vector* sequences, which is primarily due to size limitation of the virion (as disclosed in the Messerle reference). In order to generate a vector using the method disclosed in the Kemble reference, one of ordinary skill in the art must first remove a stretch of unessential viral DNA before the virus can accommodate additional vector DNA. The Kemble reference uses the entire genome, and does not identify or omit unessential virus DNA in order to resolve the size limit constraints described above.

Thus, it is evident that the adaptation of the technique of Kemble would require more than simply using BACs instead of cosmids. The Office fails to identify the aforementioned adaptations of the cited references that are required to arrive at the present invention.

In view of the foregoing, performing the method of the Kemble reference using the BACs disclosed in the Messerle reference instead of cosmids does not result in the presently claimed BAC. The Kemble reference does not disclose or suggest any method that would be useful to solve the problem underlying the present invention, i.e., how to get an infectious herpes virus genome into a BAC.

Indeed, the differences between the Kemble reference and the claimed invention have important practical implications. In order to produce an altered/mutated/recombinant virus following the protocol of the Kemble reference, the following steps are required:

1. selection of multiple vectors with overlapping inserts and modifying one of them to implement a desired modification,

2. co-transfection of a mixture of overlapping inserts resulting in multiple recombination events in eukaryotic cells,

3. isolation and purification of recombinant virus from plaques, as different plaques may contain different recombinants, and one plaque may contain a mixture of different recombinants, and

4. verification of the integrity of recombinant virus and the presence of the desired modification.

The Office fails to identify the reasons why one of ordinary skill in the art would have made the aforementioned modifications to the methods disclosed in the cited references that are required to arrive at the present invention. The presently claimed infectious BAC allows for the modification of the BAC in *E.coli* cells, without requiring any further recombination events to generate a modified virus. In addition, the presently claimed infectious BAC is clonal (i.e., pure because one colony of *E.coli* represents the uptake of one single plasmid). In contrast, obtaining a pure virus using a heterogeneous mixture of modified viruses isolated from plaques as the starting material (as disclosed in the Kemble reference) requires several rounds of infection and purification.

The Office Action has failed to analyze each of the cited references as a whole, and has used impermissible hindsight in establishing motivation to combine the teachings of the cited references. As stated in the Manual of Patent Examining Procedure (M.P.E.P.) at Section 2141.02 (emphasis in original): "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)."

None of the secondary references cited by the Office Action compensates for the aforementioned deficiencies of the Messerle and Kemble references. In this respect, none of the Ehtisham, Gage, Chen, and Luckow references discloses or suggests a BAC containing all genes essential for the generation of an infectious herpes virus in a host cell, wherein the host cell does not contain any herpes virus genes or herpes virus proteins.

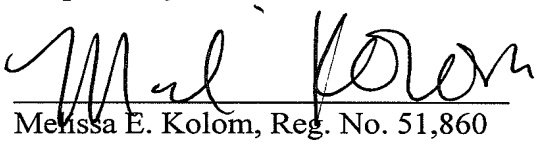
For purposes of considering the obviousness rejections, there is no need to consider any objective evidence of nonobviousness.

Considering all of the Graham factors together, it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combination of cited references. Accordingly, the obviousness rejections under Section 103 should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,



Melissa E. Kolom, Reg. No. 51,860
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

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